

REMARKS

Claims 1-7, 11, 13-14, and 16-36 were pending in the instant application. Claims 1-6, 11, and 17-28 have been withdrawn without prejudice as being drawn to non-elected subject matter. Claims 7, 13, 14, 16, 29-32, and 34 have been amended to specifically point out and distinctly claim that which the Applicants regard as the invention. Support for claims 7, 13, 14, and 16 can be found in the specification, for example, at page 9, line 31 to page 10, line 8; page 29, line 9 to page 30, line 20; p. 59, line 23 to page 60, line 6; page 62, lines 16 to 21. Support for claims 29-32 can be found in the specification, for example, at page 99, lines 16 to 24. Claim 34 has been amended to delete the second period (.) at the end of the sentence, as suggested by the Examiner. No new matter has been added by these amendments.

Reconsideration and allowance of the present application in view of the remarks below are respectfully requested.

1. OBJECTIONS FOR INFORMALITIES:

The Examiner has objected to the priority claim because it does not include the current status of the parent application. Applicants have amended the priority claim in the specification to include that Application No. 09/385,219, filed August 27, 1999, to which this application claims priority, is now Patent No. 6,720,181.

The Examiner has objected to the reference in the specification to a hyperlink and/or other forms of browser-executable code as an improper incorporation by reference. Applicants have appropriately deleted all references to hyperlinks that are present in the specification.

The Examiner has objected to the specification and the drawings for failing to identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:". Applicants have submitted a Substitute Sequence Listing listing these sequences in computer readable form and paper copy. Applicants have also incorporated these sequence identifiers in the figure legend in the specification. Pursuant to 37 C.F.R. § 1.821(f), it is hereby stated that the Sequence Listing content of the paper and computer readable copy of the Sequence Listing are the same and include no new matter. Accordingly, the objections to the specification and the figures have been overcome.

2. OBJECTIONS TO THE CLAIMS:

The Examiner has objected to the term “both” in claim 7. Applicants have deleted the term “both” pursuant to the Examiner’s suggestion.

The Examiner has objected to claim 34, as ending with two periods (..). Applicants have deleted the second period (.) at the end of claim 34, pursuant to the Examiner’s suggestion.

It is respectfully submitted that all objections have been overcome and should therefore be withdrawn.

3. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. *Standard Oil Co. v. American Cyanamide Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986).

The Examiner alleged that claims 7, 13 (claims 29, 31, 33, and 35 dependent therefrom, 14, and 16 (claims 30, 32, 34, and 36 dependent therefrom) are indefinite in the recitation of “Fbpl”. Claims 7, 13, 14, and 16 have been amended to recite “FBP1” instead of “Fbpl”. It is clear from the specification that “FBP” is a term synonymous with “F-box protein” and refers to a peptide, polypeptide, or protein which contains a F-box motif (*see, e.g.*, the specification at p. 11, *ll.* 21 to 22). It is also clear from the specification that the FBP1 protein includes those gene products encoded by the FBP1 gene sequences which comprise nucleic acid molecules containing the DNA sequences of SEQ ID NO:1 and nucleic acid molecules that can hybridize to the DNA sequence of FBP1 under stringent conditions. (*see, e.g.*, the specification at p. 39, *ll.* 16 to 19; p. 29, *l.* 19 to p.30, *l.* 31; Figure 3). Accordingly, Applicants submit that the claims are definite.

The Examiner alleged that claims 7, 13 (claims 29, 31, 33, and 35 dependent therefrom), 14, and 16 (claims 30, 32, 34, and 36 dependent therefrom) are indefinite for providing insufficient antecedent basis for “the activity”, as recited in the claims. In order to

expedite prosecution of the application, claims 7, 13, 14, and 16 have been amended to recite “FBP1 or β Trcp2 activity”. Accordingly, the rejection for insufficient antecedent basis for “the activity” is moot in view of the present claim amendment.

The Examiner further alleged that it is unclear as to the activity that is being intended by the claims. Amended claim 14 relates to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising contacting a cell or cell extract expressing FBP1, β Trcp2, and $\text{I}\kappa\text{B}\alpha$, with a compound and determining the ability of the compound to modulate FBP1 or β Trcp2 activity. The instant specification teaches that E3 ubiquitin ligases, which are key enzymes involved in the ubiquitin-mediated proteolysis of proteins are comprised of three subunits: Cdc53, Skp1 and an F-box protein (FBP) and that the interaction of the E3 ubiquitin ligases with target substrates (proteins targeted for degradation) occurs via the FBP (*see, e.g.*, the specification at p. 87, *l.* 27 to p. 88, *l.* 5). The instant specification further teaches that FBP1 and β Trcp2 are FBPs that have substrate specificity for $\text{I}\kappa\text{B}\alpha$ and promote $\text{I}\kappa\text{B}\alpha$ degradation (*see, e.g.*, the specification at p. 4, *ll.* 22 to p. 5, *ll.* 26; p. 87, *l.* 27 to p. 88, *l.* 5). Thus, when FBP activity is inhibited, degradation of $\text{I}\kappa\text{B}\alpha$ will be inhibited and higher levels of $\text{I}\kappa\text{B}\alpha$ protein will be detected as compared to a cell with normal FBP activity. Likewise, if FBP activity is enhanced, degradation of $\text{I}\kappa\text{B}\alpha$ will be enhanced and lower levels of $\text{I}\kappa\text{B}\alpha$ protein will be detected as compared to a cell with normal FBP activity. The instant specification teaches that FBP1 and β Trcp2 activity can be determined by different methods, for example, detecting binding between FBP1 and $\text{I}\kappa\text{B}\alpha$ or β Trcp2 and $\text{I}\kappa\text{B}\alpha$, by detecting ubiquitination of $\text{I}\kappa\text{B}\alpha$, or by detecting a change in the protein levels of $\text{I}\kappa\text{B}\alpha$ (*see, e.g.*, the specification at p. 9, *l.* 31 to p. 10, *l.* 8; p. 91, *l.* 20 to p. 92, *l.* 3; p. 70, *ll.* 22 to 28). Thus, Applicants submit that “FBP1 activity” or “ β Trcp2 activity” is clear in light of the support in the instant specification and as such, the rejection should be withdrawn.

The Examiner alleged that claims 7, 13 (claims 29, 31, 33, and 35 dependent therefrom), 14, and 16 (claims 30, 32, 34, and 36 dependent therefrom) are indefinite in the recitation of “Fbp1” and “ β Trcp2” as it is unclear from the specification and the claims as to the scope of polypeptides that are intended as being encompassed by the terms “Fbp1” and “ β Trcp2”. The claims of the instant application are drawn to a genus of FBP1 and β Trcp2 proteins that have a specific and required activity – that of an F box protein subunit which targets $\text{I}\kappa\text{B}\alpha$ for degradation. One skilled in the art would understand that in order for the

FBP1 to be functional, the species of FBP1 proteins that are encompassed by the claims must be structurally similar. The instant specification teaches that an FBP gene comprises any DNA sequence that hybridizes to the complement of the DNA sequences that encode the amino acid sequences of an FBP protein, such as FBP1, under stringent conditions and encodes a gene product functionally equivalent to an FBP gene product (*see, e.g.*, the specification at p. 30, *ll.* 20 to 31). It would be clear to one skilled in the art that not all sequences that hybridize to the complement of SEQ ID NO:1 are encompassed by the claims – only those that bind to substrate I κ B α and target I κ B α for degradation. Furthermore, the instant specification incorporates in its entirety Koike *et al.*, 2000, *Biochem. Biophys. Res. Comm.*, 269:103-109 (“Koike”), which discloses the DNA sequences and amino acid sequences of three isoforms of β Trcp2 (*see, e.g.*, the specification at p. 5, *ll.* 15 to 26). One skilled in the art would know that minor variations in the sequence of β Trcp2 will still yield β Trcp2 species that are functional in accordance with the present method of the invention. Thus, Applicants submit that it is clear from the specification and the amended claims as to the scope of polypeptides that are intended as being encompassed by the terms “Fbp1” and “ β Trcp2” and the rejection should be withdrawn.

The Examiner alleged that the term “test compound or compounds” as recited in claim 14 (claims 16, 30, 32, 34, and 36 depending therefrom) is confusing. Without making any admission as to the merits of the Examiner’s rejection, Applicants have amended claim 14 to eliminate the term “test compound or compounds”. As such, the rejection is moot in view of the present claim amendments.

In view of the foregoing remarks and claim amendments, Applicants respectfully request that the rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. § 112, second paragraph, be withdrawn.

4. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner alleged that that the specification discloses only a single representative species of Fbp1 polypeptides and β Trcp2 polypeptides and that the specification fails to describe any additional representative species of the recited genus of polypeptides or activities thereof that can be identified. Applicants respectfully submit that the currently pending claims contain subject matter that was described in the specification in such a way to convey to one skilled

in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The factual inquiry of whether there is sufficient written description under 35 U.S.C. § 112 is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ 2d 1111, 1117 (Fed. Cir. 1991). Disclosure of sufficiently detailed, relevant identifying characteristics, *i.e.*, structure, physical, and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or combination of such characteristics can provide evidence that Applicant was in possession of the claimed invention. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d at 964, 63 USPQ2d at 1613 (Fed. Cir. 2002).

The claims of the instant application are drawn to a genus of FBP1 and β Trcp2 proteins that have a specific and required activity – that of an F box protein subunit which targets I κ B α for degradation. One skilled in the art would understand that in order for the FBP1 and β Trcp2 to be functional, the species of FBP1 proteins that are encompassed by the claims must be structurally similar. The structural features and domains of F box proteins that are important to F box protein function had been extensively studied and were well known in the art at the time the instant application was filed (*see, e.g.*, the specification at p. 2, *l.* 21 to p. 6, *l.* 16). The instant specification teaches that FBP1 and β Trcp2 activity can be determined by many methods, for example, by detecting binding between FBP1 and I κ B α or β Trcp2 and I κ B α , by detecting ubiquitination of I κ B α , or by detecting a change in the protein levels of I κ B α (*see, e.g.*, the specification at p. 9, *l.* 31 to p. 10, *l.* 8; p. 91, *l.* 20 to p. 92, *l.* 3; p. 70, *ll.* 22 to 28). There was a high level of skill in the art of biochemistry at the time the application was filed, such that techniques that detect protein-protein interaction, protein levels, and ubiquitination in a cell or cell extract were well known and routine in the art.

Applicants submit that the instant specification provides clear written description for the species encompassed by FBP1. For example, the instant specification teaches that the FBP1 gene comprises a nucleic acid molecule containing the DNA sequences as shown in Figure 3 (SEQ ID NO:1) and any DNA sequence that encodes a polypeptide containing the amino acid sequence of FBP1 as shown in Figure 3A (SEQ ID NO:2) (*see, e.g.*, the

specification at p. 29, *ll.* 10 to 11; p. 29, *ll.* 31-32). The instant specification further teaches that an FBP gene comprises any DNA sequence that hybridizes to the complement of the DNA sequences that encode the amino acid sequences of an FBP protein, such as FBP1, under highly stringent conditions and encodes a gene product functionally equivalent to an FBP gene product (*see, e.g.*, the specification at p. 30, *ll.* 20 to 31). Such methods of hybridization are well known in the art (*see, e.g.*, the specification at p. 30, *ll.* 20 to 26, citing to Ausubel et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. 1, Green Publishing Associates, Inc., and John Wiley & Son, Inc., New York, at p. 2.10.3). It would be clear to one skilled in the art that not all sequences that hybridize to the complement of SEQ ID NO:1 are encompassed by the claims – only those that target IκBα for degradation.

Applicants further submit that the instant specification provides clear written description for the species encompassed by βTrcp2. The instant specification incorporates in its entirety Koike *et al.*, 2000, *Biochem. Biophys. Res. Comm.*, 269:103-109 (“Koike”), which discloses the DNA sequences and amino acid sequences of three isoforms of βTrcp2 (*see, e.g.*, the specification at p. 5, *ll.* 15 to 26). One skilled in the art would know that minor variations in the sequence of βTrcp2 will still yield βTrcp2 species that are functional in accordance with the present method of the invention.

In addition to the support provided in the instant specification for DNA hybridization techniques, there was a high level of skill in the art of molecular biology at the time the application was filed. All the methods needed to practice the claimed invention including DNA hybridization techniques were well known and routine in the art. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g.*, *M.P.E.P.* 2163 I. citing to *Moba, B.V. v. Diamond Automation Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. Furthermore, what is conventional or well known to one of skill in the art need not be disclosed in detail and, where the level of knowledge and skill in the art is high, a written description question should not be raised. *See, e.g.*, *Capon v. Eshhar*, 418 F.3d 1349, at 1357 (Fed. Cir. 2005).

Applicants additionally direct the Examiner’s attention to example 9, at page 35 of the Synopsis of Application of Written Description Guidelines, available at <http://www.uspto.gov/web/patents/guides.htm> (“Application Guidelines”). In Example 9 of the Application Guidelines, the specification discloses a single cDNA that encodes a protein

of a particular function. A stringent hybridization was performed and several nucleic acids that encode proteins that perform the same function were isolated. It is stated in the Application Guidelines that a person of skill in the art would not expect substantial variation among species because the hybridization conditions would set forth structurally similar cDNAs. Similarly in the present invention, a skilled artisan would not expect substantial variation among the species because the hybridization conditions as set forth in the claims would yield structurally similar FBP1 proteins. Thus, as in Example 9 of the Application Guidelines, a skilled artisan would accept that a representative number of species is disclosed, since stringent hybridization conditions for FBP1 in combination with the function of FBP1 and β Trcp2 proteins and high level of skill and knowledge in the art of molecular biology and F box protein biochemistry are adequate to determine that Applicants are in possession of the claimed invention.

Applicants respectfully submit that the requirement of written description is met and respectfully request that the rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. 112, first paragraph, be withdrawn.

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner alleged that the specification does not reasonably provide enablement for a method of using all FBP1 and β Trcp2 proteins encompassed by the claims. In particular, the Examiner alleged that neither the specification nor the state of the art at the time the application was filed provided the necessary guidance for altering the amino acid sequences of FBP1 and β Trcp2 with an expectation of obtaining a polypeptide having the activity of FBP1 and β Trcp2 that is specified in the claims. Applicants respectfully submit that, for the reasons discussed below and according to the applicable case law, the instant specification does fully enable one of skill in the art to make and use all FBP1 and β Trcp2 proteins corresponding to the scope of the presently pending claims.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Teletronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (“a patent need not teach, and preferably omits, what is well known in the art.”). Further, one skilled in the art is presumed to use the information

available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) (“A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation.”). These enablement rules preclude the need for the patent applicant to “set forth every minute detail regarding the invention.” *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Applicants submit that the instant specification coupled with the information which was readily available to the skilled artisan at the time the instant application was filed provides considerable direction and guidance on how to make and use the claimed invention. The present invention relates to a screening method for identifying compounds useful for the treatment of proliferative and differentiative disorders by determining the ability of a compound to modulate FBP1 or β Trcp2 activity, wherein FBP1 and β Trcp2 activity is characterized by degradation of I κ B α . The screening method of the present invention comprises contacting a compound with a cell or cell extract expressing FBP1, β Trcp2, and I κ B α and determining the ability of the compound to modulate FBP1 or β Trcp2 activity. Thus, the screening method must be comprised of functionally active FBP1, β Trcp2, and I κ B α proteins, such that I κ B α can be degraded. As discussed previously, the instant specification provides full support for the nucleotide and amino acid sequences encompassed by the claimed invention, along with the hybridization assays used to make the FBP1 species (*see*, the present paper at p.17). Furthermore, the structural features of F box proteins, along with methods than can be used to measure FBP1 and β Trcp2’s functional activities are described in the instant specification and were well known and routine to those skilled in the art at the time the instant application was filed (*see*, the present paper at pp. 16 to 17). Thus, the Examiner’s contention that the specification fails to disclose any specific guidance for altering the FBP1 and β Trcp2 proteins with an expectation that the resulting variants as encompassed by the claims will maintain the desired activity, is simply incorrect. Once functional FBP1 and β Trcp2 species are identified, they can be used in accordance with the screening methods of the instant invention to identify compounds that are useful for the treatment of proliferative and differentiative disorders.

According to *M.P.E.P.* § 2164.02, “[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if

one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.” In the instant case, in view of the level of skill, state of the art, and the information in the specification, one skilled in the art would recognize and appreciate that the teachings of the specification as exemplified for one species of FBP1 are equally applicable to other FBP1 and β Ttcp2 species with similar functional activities, given the similarity in structure, and would not require undue experimentation.

Thus, Applicants submit that the specification, coupled with the state of the art as of the effective filing date of the instant application, fully enables one of skill in the art to make, use, and practice the invention as claimed without undue experimentation. Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

5. CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Yaron et al., 1997. *EMBO J.* 16:6488-6494 (“Yaron 1997”) and by Yaron et al., 1998. *Nature*. 396:590-594 (“Yaron 1998”). Applicants respectfully submit that both Yaron 1997 and Yaron 1998 fail to teach or suggest the claimed methods. In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628 (Fed. Cir. 1987).

Yaron 1997 teaches that I κ B α is targeted for ubiquitin-dependent degradation when it is phosphorylated on ser 32 and ser 36. Yaron 1997 teaches *in vitro* ubiquitination assays in which NF- κ B associated [35 S] I κ B α or wild-type [35 S] I κ B α was subjected to *in vitro* ubiquitination in HeLa cell extracts in the presence of ubiquitin, ATP γ S and/or various synthetic inhibitory peptides that span the phosphorylation sites on I κ B α (*see*, Yaron 1997 at page 6493, col. 1). The presence of ubiquitinated I κ B α is then measured by 9% SDS-PAGE followed by fluorography (*see*, Yaron 1997 at page 6493, col. 1). Yaron 1997 also teaches a complementary ubiquitin-dependent *in vitro* degradation assay in which phosphorylated I κ B α was immunopurified from stimulated Jurkat cells and subjected to ubiquitination in a reticulocyte assay in the presence of ATP and various synthetic inhibitory peptides that span the phosphorylation sites on I κ B α (*see*, Yaron 1997, p.6488, col. 2 to p. 6489, col. 1; Figure 4). I κ B α was detected by Western blot analysis with a specific rabbit antiserum (*see*, Yaron 1997, p.6488, col. 2 to p. 6489, col. 1; Figure 4).

Yaron 1997 fails to teach or suggest a screening method for identifying compounds

useful for the treatment of proliferative and differentiative disorders comprising determining the ability of the compounds to modulate FBP1 or β Trcp2 activity. There is no teaching whatsoever of FBP1 or β Trcp2 being participants in any of the methods or assays that are taught in Yaron 1997, let alone a teaching of a screening method for compounds useful for the treatment of proliferative and differentiative disorders by detecting a change in the activity of FBP1 or β Trcp2 .

Even assuming *arguendo* that FBP1 or β Trcp2 are present in the cell extracts of the ubiquitination assays discussed in Yaron 1997, Yaron 1997 does not teach a method of screening for compounds useful for treatment of cancer, nor does it teach compounds that have the ability to modulate the activity of FBP1 or β Trcp2. As discussed above, Yaron 1997 teaches methods for assaying ubiquitin-mediated degradation in cell extracts in the presence of ATP and/or synthetic inhibitory peptides and subsequently detects ubiquitination or protein levels of $\text{I}\kappa\text{B}\alpha$. Thus, Yaron teaches how the phosphorylation state of $\text{I}\kappa\text{B}\alpha$ affects $\text{I}\kappa\text{B}\alpha$ ubiquitination and degradation and is in no way concerned with a screening method that uses the interaction of FBP1 and $\text{I}\kappa\text{B}\alpha$ or β Trcp2 and $\text{I}\kappa\text{B}\alpha$ to select compounds that are useful for the treatment of proliferative and differentiative disorders. As such, Yaron 1997 cannot anticipate the instant claims.

Yaron 1998 also fails to anticipate the claims. Yaron 1998 teaches the isolation of a $\text{I}\kappa\text{B}\alpha$ -ubiquitin ligase from HeLa cells by single step immunoaffinity purification. Using nanoelectrospray mass spectrometry, Yaron 1998 identifies a β Trcp subunit of the ligase, named $\text{E3RS}^{\text{I}\kappa\text{B}}$, that binds specifically to $\text{I}\kappa\text{B}\alpha$ via a degradation motif and promotes its *in vitro* ubiquitination. FBP1 or β Trcp2 are mentioned nowhere in Yaron 1998. Even assuming *arguendo* that $\text{E3RS}^{\text{I}\kappa\text{B}}$ is a species of FBP1 or β Trcp2, Yaron 1998 is not directed at determining whether a compound can modulate the activity of FBP1 or β Trcp2. Yaron 1998 teaches *in vitro* ubiquitination assays in which phosphorylated NF- κB - $\text{I}\kappa\text{B}\alpha$ complex is incubated with ubiquitin, purified E1 and E2, ATP and an inhibitory phosphopeptide (pp10) that binds to the degradation motif of $\text{I}\kappa\text{B}\alpha$ (*see*, Yaron 1998 at p. 591, col. 1). These assays were not performed in order to screen for compounds that can modulate FBP1 or β Trcp2 activity, as required by the claims, but to help isolate a $\text{I}\kappa\text{B}\alpha$ specific E3 ligase and F-box protein. These assays also were performed in a cell free system, whereas the claims of the instant invention require contact with a cell or cell extract. Furthermore, these binding assays can hardly be classified as screening methods that are aimed at identifying compounds that

are useful for the treatment of proliferative and differentiative disorders by detecting a change in the activity of FBP1 or β Trecp2, but rather methods aimed at confirming the specificity of E3RS^{I κ B} binding to I κ B α . Thus, Yaron 1998 fails to teach or suggest every element of the instant invention and as such cannot anticipate the claims.

In view of the above remarks, Applicants submit that the pending claims satisfy the requirements of 35 U.S.C. §102(b) and respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the formal objections have been obviated and rejections to the pending claims should be withdrawn. No new matter has been added by these amendments. Applicants respectfully submit that all claims are now in condition for allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

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